CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020887

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

DUPLICATE

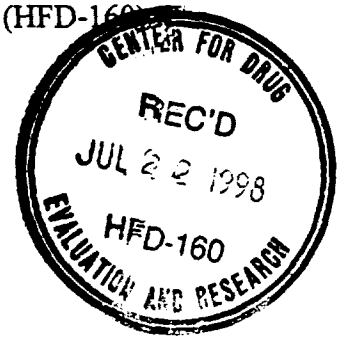
Diatide, Inc.

9 Delta Drive • Londonderry, New Hampshire 03053
(603) 437-8970 • FAX (603) 437-8977

July 21, 1998

NDA ORIG AMENDMENT
BM

Catalina Ferre-Hockensmith
Division of Medical Imaging and Radiopharmaceutical Drug Products (HFD-160)
Center for Drug Evaluation and Research
Food & Drug Administration
Parklawn Building, Room 18B-08
5600 Fishers Lane
Rockville, MD 20857



RE: NDA 20-887
AcuTect™
Kit for the Preparation of Technetium Tc 99m Apcitide

Dear Ms. Ferre-Hockensmith:

Please refer to your fax dated July 15, 1998 which requested clarification on several Phase 4 commitments for NDA 20-887. Your requests are restated below followed by our responses.

Sincerely,

J. Kris Piper
Senior Director Regulatory Affairs

JKP/slb

ORIGINAL N 21

Diatide, Inc.

9 Delta Drive • Londonderry, New Hampshire 03053
(603) 437-8970 • FAX (603) 437-8977

March 13, 1998

APPEARS THIS WAY
ON ORIGINAL

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER / ☒ N.A.I. ☐ MEMO
CSO INITIALS
3/18/98
DATE

Division of Medical Imaging and
Radiopharmaceutical Drug Products (HFD-160)
Center for Drug Evaluation and Research
U. S. Food and Drug Administration
Parklawn Building, Room 18B-08
5600 Fishers Lane
Rockville, Maryland 20857

Re: NDA 20,887 - AMENDMENT
AcuTect™ Kit for the Preparation of Technetium Tc 99m Apcitide Injection

Amendment: Response to Approvable Letter

APPEARS THIS WAY
ON ORIGINAL

Dear Sir or Madam:

Please refer to your letter dated February 20, 1998, regarding the approvable status of the new drug application for AcuTect. This amendment contains the additional information requested in your letter and provides the Phase 4 commitments that you require.

We trust that the information provided herein satisfies the agency's concerns regarding AcuTect. We look forward to receiving your comments on our proposed protocols and studies and to a speedy approval of this NDA.

Sincerely,

APPEARS THIS WAY
ON ORIGINAL

J. Kris Piper
Senior Director Regulatory Affairs

JKP/slb

enclosures

CENTER FOR DRUG
RECD
MAR 1 6 1998
160
EVALUATION AND RESEARCH

DUPLICATE

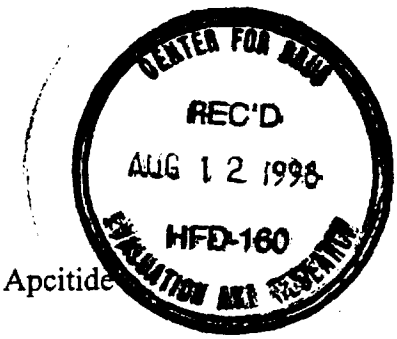
Diatide, Inc.

9 Delta Drive • Londonderry, New Hampshire 03053
(603) 437-8970 • FAX (603) 437-8977

SUPPL NEW CORRESP

August 11, 1998

Catalina Ferre-Hockensmith
Division of Medical Imaging and Radiopharmaceutical Drug Products (HFD-160)
Center for Drug Evaluation and Research
Food & Drug Administration
Parklawn Building, Room 18B-08
5600 Fishers Lane
Rockville, MD 20857



RE: NDA 20-887
AcuTect™
Kit for the Preparation of Technetium Tc 99m Apcitide

Dear Ms. Ferre-Hockensmith:

As requested, we are providing the following statements regarding the manufacturing, marketing and distribution of AcuTect:

a) AcuTect kit is manufactured for Diatide, Inc. by Dr. Rentschler Biotechnolgie GmbH, Laupheim, Germany.

   As required by 21 CFR 201.1, the vial and carton labels state that the product is "Manufactured for Diatide, Inc."

b) Under contractural agreement, AcuTect will be marketed and distributed in the United States by both Diatide, Inc. and Nycomed-Amersham.

   Both companies' names are included on the vial and carton labels to indicate this.

Please contact me if you require additional information.

Sincerely,

APPEARS THIS WAY
ON ORIGINAL

J. Kris Piper
Senior Director Regulatory Affairs

JKP/slb

DIVISION DIRECTOR MEMORANDUM TO THE FILE

NDA:	20,887
DRUG:	AcuTect™ Kit for the Preparation of Technetium ~~Tc~~99m Apcitide
INDICATION:	Detection of Acute Venous Thrombosis
CATEGORY:	1P - Response to Approvable Letter
SPONSOR:	Diatide, Inc.
SUBMITTED:	March 16, 1998
COMPLETED:	August 20, 1998
PDUFA DATE:	September 16, 1998

RELATED REVIEWS:

Clinical - AE Jones, M.D., 6/8/98
Clinical Pharmacology - D Udo, PhD 3/13/98
Pharmacology - A Laniyonu, PhD, 6/12/98
Division Memoranda - P Love, M.D., 1/20/98, 2/12/98

RELATED CLEARANCE: EER - Acceptable 6/12/98

PROJECT MANAGER: Catallina Ferre-Hockensmith

BACKGROUND: AcuTect™ Kit for the preparation of Technetium Tc99m Apcitide (a radioactive synthetic peptide to bind receptors on activated platelets (GPIIAIIIB)) was originally submitted on August 20, 1997 with the proposed indication of detecting acute venous thrombosis during SPECT imaging (single photon emission computerized tomography). AcuTect™ is designated as a priority new drug because the diagnosis of acute venous thrombosis can not be made directly with any existing diagnostic modality. The other available modalities, contrast venography and ultrasound, provide anatomic information only. Also, ultrasound is not useful in the calf or pelvis and inconclusive ultrasound images can delay the diagnosis and increase the risk of embolic phenomena.

On February 9, 1998 the NDA was presented to the Medical Imaging Drug Advisory Committee (MIDAC). As outlined in division summary memoranda of 1/20 & 2/12/98, the MIDAC considered a number of issues including the limited usefulness of an agreement study that does not have a definitive reference standard of truth, the post hoc use of a research center to re-read the contrast venography, and the lack of a clinical correlation with the AcuTect™ image interpretations (e.g., are the true negatives really negative, can treatment be withheld). The committee recommended an approval with additional studies on clinical outcomes.

Critical to the division decision is the fact that AcuTect™'s primary outcome variable of agreement with an imperfect reference standard (contrast venography) diminished the ability to derive direct or implied clinical usage information. The matched positive AcuTect™ and contrast venography results, and the matched negative AcuTect™ and contrast venography results suggest that physicians can use the positive results to guide the decision to treat. The negative AcuTect™ results, however, are not strong enough to withhold treatment. It is important to determine how AcuTect™ should be used in relationship to ultrasound or contrast venography in acutely symptomatic patients. Therefore, this issue should be clear in the drug

labeling.

Labeling: Labeling was sent with the February 20, 1998 approvable letter. The label requested verification of patient numbers, and updates with the Hamilton image criteria. The Hamilton criteria were clarified during the review and are incorporated in the labeling. Also, the sponsor requested a few labeling edits or deletions. These were considered by the review team. Generally, those that were editorial were accepted. Promotional statements were deleted. Also, the review team clarified the data presentation in the clinical trials section. Final labeling is in the Labeling Section of the Action Package.

ACTION: APPROVAL
LETTER: List Phase 4 commitments and AE monitoring card system

/S/ 8/24/98
Patricia Y. Love, M.D.

DIVISION DIRECTOR
POST ADVISORY COMMITTEE MEMORANDUM TO THE FILE

NDA:	**20,887**
DRUG:	**AcuTect Kit for the preparation of Technetium Tc99m Apcitide**
INDICATION:	**For the detection of acute venous thrombosis**
CATEGORY:	**1P - Original Submission**
SPONSOR:	**Diatide, Inc.**
SUBMITTED:	**August 20, 1997**
ADVISORY COMMITTEE:	**February 09, 1998**
PREPARED:	**February 12, 1998**
PDUFA DATE:	**February 20, 1998**

/S/ 2/12/98

On February 9, 1998 the AcuTect NDA was presented to the Medical Imaging Advisory Committee. The official transcript is pending at the time of this writing. The official questions are attached to this memo. The committee chose to provide consensus or general comments on all of the questions expect for the questions of whether to accept study # 280-32A and B (question # III.c. 1 & 2), and whether to recommend the application as approvable (question VI a). The vote was to accept each study with scores for study A of yes -11, and no - 1. For study B the scores were yes - 7, and no - 5. Also, the committee voted to recommend the application as approvable with scores of yes - 7, no - 4, and abstention - 1.

The background discussion focused on several themes, the priority nature of the drug, the imperfect standard diagnostic method, and the implication of the agreement data. Specifically, the committee agreed that the agency's designation of priority is appropriate. The diagnosis of acute venous thrombosis can not be made directly with any existing diagnostic modality. Contrast venography and ultrasound provide anatomic information only. Also, ultrasound is not useful in the calf or pelvis. Plus, inconclusive ultrasound images can delay the diagnosis for several days and, thereby, increase the risk of embolic phenomena. These perspectives appeared to affect the recommendation of approvable.

The issue of the imperfect standard diagnostic method was somewhat controversial. The discussion considered the post hoc nature of the Hamilton read versus the clinical need for the Hamilton read. All of the physicians felt that the clinical reason for using the Hamilton center was appropriate because they are the western hemisphere's leading center and standardized criteria are needed. Also, the Hamilton center provided the standard of truth contrast venography interpretations for two FDA approved drugs (Lovenox and Normoflo). The original blinded contrast venography was completed by radiologists from different centers without any *a priori* reading criteria. The statisticians acknowledged the post-hoc problems, but variably deferred to the clinical need for the Hamilton reading. The mixed vote for study B reflects these concerns. Also, for both study A and B the acceptance is based upon meeting the statistical primary outcome measure. For study A the primary outcome measure is met in comparison to either blinded contrast venography method. For study B it is met in comparison to the Hamilton venography.

Another controversial issue was the implication of the agreement primary outcome measure. The primary outcome measure is at least a 60% agreement rate of Acutest with contrast venography; e.g. the rate at which both the positive or negative interpretations agreed. The agreement, therefore, mixes the true positive, true negative, false positive and false negatives. Also, the agreement of at least 60% with an imperfect standard limited the reliability of the negative Acutest images. Therefore, several committee members felt that the agreement data provided initial data but did not clarify how to use the image results in the diagnostic or patient management setting. For example, could a patient be sent home if the images were negative? Also, is Acutest a stand alone, does it really replace venography, should it be used in conjunction with ultrasound? Several hypothesis were mentioned by the members, but the committee noted that these scenarios were not studied. Therefore, clinical outcome studies were recommended.

At various points throughout the meeting the committee asked for advice on the implication of "approvable". In my opinion, this was not understood fully because at the end of the meeting the committee was asked if there was more information that was needed before approval. A vote was not taken, but the comments were to obtain more safety data on hypersensitivity and for longer monitoring, and to complete the clinical outcomes studies. This is inconsistent with our existing regulatory context of approvable; i.e, if major new studies are needed, then the application is not approved.

After the meeting, these issues were considered with Bronwyn Collier, Deputy Director of ODE-III and Dr. M. Lumpkin, Deputy Director, CDER.

CONCLUSION: APPROVABLE with the issues outlined above and with labeling revisions as attached to the draft letter.

Item 13. PATENT INFORMATION

[21 U.S.C. 355 (b) and (c)]

The required patent information is presented on the following page.

Item 14. PATENT CERTIFICATION

[21 U.S.C. 355 (b) (2) or (j) (2) (A)]

APPEARS THIS WAY
ON ORIGINAL

Diatide, Inc. certifies that Patent Nos. 5,508,020; 5,045,815; 5,443,815; 5,185,433 and 5,066,716 will not be infringed by the manufacture, use or sale of Kit for the Preparation of Technetium Tc 99m Apcitide for which this application is submitted.

Diatide, Inc. will comply with the requirements under 21 CFR 314.52 (a) with respect to providing notice to each owner of the patent or their representative.

To the best of Diatide's knowledge all patents which pertain to the drug, drug product or method of use for the product which is the subject of this application are either assigned to Diatide or have been licensed to Diatide by the patent holder.

On behalf of Diatide, Inc., I certify that the above statement is accurate and correct.

APPEARS THIS WAY
ON ORIGINAL

J. Kris Piper
Senior Director Regulatory Affairs and Quality Assurance
Diatide, Inc.

atide, Inc.

9 Delta Drive • Londonderry, New Hampshire 03053
(603) 437-8970 • FAX (603) 437-8977

APPEARS THIS WAY
ON ORIGINAL

Declaration and Submission of Patent Information Pursuant to 21 U.S.C. sec. 355(b) and 21 C.F.R. sec. 314.53 (c) for NDA Directed to Kit for the Preparation of Technetium Tc 99m Apcitide

Patent Number	Expiration Date	Type of Patent	Name of Patent Owner
US 5,508,020	4/16/2013	Drug	Assigned to: Diatide, Inc., Londonderry, NH USA 03053
US 5,645,815	7/8/2014	Drug, Drug Product, and Method of Use	Assigned to: Diatide, Inc., Londonderry, NH USA 03053
US 5,443,815	8/22/2012	Drug Product	Assigned to: Diatide, Inc., Londonderry, NH USA 03053
US 5,185,433	4/9/2010	Drug	Assigned to: Centocor, Inc., Malvern, PA Licensed to Diatide, Inc., Londonderry, NH USA 03053
US 5,066,716	12/13/2008	Drug	Assigned to: United States of America as represented by the Secretary of the Department of Health and Human Services Licensed to Diatide, Inc., Londonderry, NH USA 03053

The undersigned declares that U.S. Pat. Nos. 5,508,020; 5,645,815; 5,443,815; 5,185,433 and 5,066,716 cover the formulation, composition, and/or method of use of Kit for the Preparation of Technetium Tc 99m Apcitide. This product is the subject of this application for which approval is being sought.

APPEARS THIS WAY
ON ORIGINAL

DIATIDE, INC.

Date: 7/17/97

Patricia A. McDaniels

By: Patricia A. McDaniels
Patent Counsel

EXCLUSIVITY SUMMARY for NDA # 20-887 SUPPL # _____

Trade Name AcuTect™ _____ Generic Name _____
Applicant Name Diatide, Inc. _____ HFD-160

Approval Date September 14, 1998

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA?
   YES /✓/ NO /__/

   b) Is it an effectiveness supplement?

   YES /__/ NO /✓/

   If yes, what type? (SE1, SE2, etc.) ____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /✓/ NO /__/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

Form OGD-011347 Revised 8/7/95; edited 8/8/95
cc: Original NDA Division File HFD-85 Mary Ann Holovac

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

d) Did the applicant request exclusivity?

YES /__/ NO /✓/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /__/ NO /✓/

If yes, NDA # _____ Drug Name_____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /__/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

APPEARS THIS WAY ON ORIGINAL

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /✓/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

APPEARS THIS WAY
ON ORIGINAL

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /✓/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

APPEARS THIS WAY
ON ORIGINAL

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

APPEARS THIS WAY ON ORIGINAL

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

APPEARS THIS WAY ON ORIGINAL

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

APPEARS THIS WAY
ON ORIGINAL

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #_____
NDA # _____ Study #_____
NDA # _____ Study #_____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #_____
NDA # _____ Study #_____
NDA # _____ Study #_____

APPEARS THIS WAY
ON ORIGINAL

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_, Study # _____

Investigation #_, Study # _____

Investigation #_, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # ____ YES /__/ NO /__/ Explain: ____

_____

Investigation #2

IND # ____ YES /__/ NO /__/ Explain: ____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /__/ Explain _____ NO /__/ Explain _____

_____ _____

_____ _____

Investigation #2 !

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

_____

/S/

_____ 8/25/98

Signature Date

Title: Consumer Safety Officer

/S/

_____ 9/4/98

Signature of Division Director Date

cc: Original NDA Division File HFD-85 Mary Ann Holovac

Item 16. DEBARMENT CERTIFICATION
[FD&C Act 306 (k) (l)]

In accordance with Section 306 (k) of the Federal Food, Drug and Cosmetic Act, Diatide, Inc., certifies that it did not and will not use in any capacity the services of any person debarred under Subsection (a) or (b) of Section 306 of the Act in connection with this application.

Diatide, Inc.

9 Delta Drive • Londonderry, New Hampshire 03053
(603) 437-8970 • FAX (603) 437-8977

NDA ORIG AMENDMENT
BL

August 10, 1998

Division of Medical Imaging and Radiopharmaceutical Drug Products (HFD-160)
Center for Drug Evaluation and Research
Food and Drug Administration
Parklawn Building, Room 18B-08
5600 Fishers Lane
Rockville, MD 20857

Attn: Catalina Ferre-Hochensmith

Re: NEW DRUG APPLICATION
NDA 20-887
AcuTect™ (Kit for the Preparation of Technetium Tc 99m Apcitide Injection)

Dear Ms. Ferre-Hockensmith:

Please find enclosed the current versions of the draft vial and carton labels for AcuTect. These labels are essentially the same as the draft labels included in the original NDA submission. Copies of the original draft labels are also enclosed for reference.

The primary changes made to the labels include repositioning of information, change in the storage temperature conditions as requested by the Chemistry reviewer, and a change in the prescription drug legend to "Rx Only" as required by the FDA Modernization Act.

We would appreciate the division's opinion on these labels so that we may proceed with printing final labeling as soon as possible. Please contact me with your comments.

Sincerely,

APPEARS THIS WAY
ON ORIGINAL

J. Kris Piper
Senior Director Regulatory Affairs

enclosures

Diatide, Inc.

9 Delta Drive • Londonderry, New Hampshire 03053
(603) 437-8970 • FAX (603) 437-8977

June 17, 1998

Catalina Ferre-Hockensmith
Division of Medical Imaging and Radiopharmaceutical Drug Products (HFD-160)
Center for Drug Evaluation and Research
Food & Drug Administration
Parklawn Building, Room 18B-08
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-887
AcuTect™
Kit for the Preparation of Technetium Tc 99m Apcitide Injection

Dear Ms. Ferre-Hockensmith:

Please refer to our telephone conference call on June 13th which included Dr. Eric Jones of the division. Dr. Jones had several comments regarding our March 13, 1998 amendment to the AcuTect NDA. Dr. Jones' comments are paraphrased below followed by our answers.

- Was there a written procedure or protocol used by the Hamilton group during their blind read of the contrast venograms

- Regarding the Adverse Event reporting card, we are interested in retrieving additional information. Please consider adding the following fields on to the card:

  - Onset time
  - List of concurrent medications
  - Description of any treatment required

- As a suggestion, would you consider incorporating into the proposed fully-occluded-vessel study in dogs use of pertechnetate alone to determine whether AcuTect can distinguish acute clot from inflammation of the vessel.

  Response

  We will take this suggestion into consideration as we develop the protocol for this proposed study

If there are any further questions regarding the AcuTect NDA or our commitments for post-approval studies, please do not hesitate to contact me.

Sincerely,

J. Kris Piper
Senior Director Regulatory Affairs

JKP/slb

enclosure

Diatide, Inc.

9 Delta Drive • Londonderry, New Hampshire 03053
(603) 437-8970 • FAX (603) 437-8977

May 28, 1998

Catalina Ferre-Hockensmith
Division of Medical Imaging and Radiopharmaceutical Drug Products (HFD-160)
Center for Drug Evaluation and Research
Food & Drug Administration
Parklawn Building, Room 18B-08
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20887
AcuTect™
Kit for the Preparation of Technetium Tc 99m Apcitide

Dear Ms. Ferre-Hockensmith:

As you requested in your telephone call of May 27, 1998, please find enclosed the raw data used to generate the figures in study R 2.79. These figures are located in Volume 1.11, page 65 of the AcuTect NDA. A copy of the report (without appendices) is also included here for reference.

Study R 2.79 was entitled *Binding of the Rhenium Complex of Apcitide to Purified Integrins $\alpha_2\beta_3$ (Fibrinogen Receptor) and $\alpha_5\beta_3$ (Vitronectin Receptor).*

In the enclosed tables, Peptide 1001 is sibapcitide (now called bibapcitide) and Peptide 1002 is the oxorhenium complex of apcitide (Re-Apcitide). Eristostatin served as the control.

Replicate samples were assayed at each concentration using the method. The values plotted in the figures were the average of each set of assay results.

Please let me know if you need any additional information.

Sincerely,

APPEARS THIS WAY
ON ORIGINAL

J. Kris Piper
Senior Director Regulatory Affairs

JKP/slb

enclosures

DIATIDE, INC.

Binding of the Rhenium Complex of Apcitide to Purified Integrins $\alpha_2\beta_3$ (Fibrinogen Receptor) and $\alpha_5\beta_3$ (Vitronectin Receptor)

Technical Report No: R2.79

Date: June 18, 1997

Prepared by: Carol A. Nelson, Ph.D.
Senior Research Pharmacologist

Signature: _____

Larry R. Bush, Ph.D.
Director, Research New Product Discovery and Evaluation

Signature: _____

Approved by: John Lister-James, Ph.D.
Senior Director of Research & Development

Signature: _____

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-887

Diatide, Inc.
9 Delta Drive
Londonderry, NH 03053

Attention: J. Kris Piper
Senior Director Regulatory Affairs

Dear Mr. Piper:

We acknowledge receipt on March 16, 1998, of your March 13, 1998, resubmission to your new drug application (NDA) for AcuTect™ Kit for the Preparation of Technetium Tc 99m Apcitide 100 ug peptide injection.

This resubmission contains additional information submitted in response to our February 20, 1998 action letter.

We consider this a complete, class 2 response to our February 20, 1998 action letter. Therefore, the user fee goal date is September 16, 1998.

If you have any questions, please contact Catalina Ferre-Hockensmith, Consumer Safety Officer, at (301) 443-7515.

Sincerely yours,

/S/

Robert K. Leedham Jr.
Supervisory Consumer Safety Officer
Division of Medical Imaging and
Radiopharmaceutical Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

RECORD OF TELEPHONE CONVERSATION/MEETING	DATE September 17, 1997
I reiterated to the firm the need to respond in a timely fashion to our requests given the compressed time frame of our review cycle for this application. They noted our concern. I requested that they direct us to or supply the normal lab values for the lab parameters monitored in the clinical studies. I also inquired as to their response to our earlier request for information (9/9/97) to Mr. Piper. Mr. Coveny stated that he had a letter in front of him that responded to our points and noted that it was dated yesterday so presumably has been sent. Mr. Coveny committed to telephoning this pm with further clarification and information. The conversation was cordial and businesslike. Cc: NDA Arch HFD-160--Ferre/Jones/Zolman APPEARS THIS WAY ON ORIGINAL	NDA NUMBER 20-887 IND NUMBER TELECON INITIATED BY [ ] APPLICANT/ SPONSOR [xx] FDA MADE [xx] BY TELEPHONE [ ] IN PERSON PRODUCT NAME Acutect FIRM NAME Diatide NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD Joseph Coveny Reg Affairs TELEPHONE 603/437-8970
SIGNATURE /S/ 9/17/97 J.R. Cheever, D.M.D., AssocDir	DIVISION HFD-160

Diatide, Inc.

9 Delta Drive • Londonderry, New Hampshire 03053
(603) 437-8970 • FAX (603) 437-8977

Via Fax

September 17, 1997

James Cheever, D.M.D.
Supervisory Consumer Safety Officer
Division of Medical Imaging and
Radiopharmaceutical Drug Products (HFD-160)
Center for Drug Evaluation and Research
U. S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

APPEARS THIS WAY
ON ORIGINAL

Re: NDA 20,857
Kit for the Preparation of Technetium Tc 99m Apcitide

Dear Doctor Cheever:

This fax responds to your request this morning for the locations of the normal ranges for clinical laboratory tests. At your recommendation in our follow up telephone conversation this afternoon, Diatide supplies the locations by fax.

The assigned medical officer may find normal ranges for in the appendixes of respective reports for the following clinical studies:

Study 280-00 Appendix 16.2, Table 22, located in NDA Volume 1.66, Pages 242-43.

Study 280-10 Appendix 16.2, Table 14, located in NDA Volume 1.28, Pages 261-63.

Study 280-22 Appendix 16.2, Table 15, located in NDA Volume 1.35, Pages 162-70.

Study 280-23 Appendix 16.2, Tables 23-24, in NDA Volume 1.69, Pages 221-27.

Clinical laboratory test normal ranges for Studies 280-11 and 280-33 were supplied electronically in SAS datasets on diskettes that accompanied the study reports. In accordance with the letter sent to FDA on September 16, 1997, (a copy of which is attached to this fax at your request in this afternoon's telephone call) that responds to FDA's request of September 9, 1997, Diatide is preparing a directory of all of the SAS datasets located on these diskettes, and will make those directories available in the next few days. In the meantime, we have supplied a printed copy of this information for Study 280-33 as another attachment to this fax. We will supply the normal range values for Study 280-11 on or before Friday this week via fax.

As an annotation to the attached table of normal-range values, all but one site in Study 280-33 used a central clinical laboratory for these tests. Normal ranges for these sites are identified in the first column (Study Site) of the table as site 9. Normal ranges for the lone site that used its own clinic's clinical laboratory are identified in the table as Study Site 1.

In accordance with our phone conversation, Diatide will send tomorrow an IND Safety Report concerning the death of one patient volunteer who participated in Study 280-11. As I mentioned over the telephone, although the death occurred on May 16, 1997, Diatide became aware of it only on September 8, 1997. This subject's death occurred more than a week after she completed uneventful participation in the study. Her death was attributed to systemic embolic disease secondary to a prosthetic mitral valve and to infective endocarditits. The clinical investigator considered it highly improbable that the investigational drug contributed to this event.

Sincerely,

Joseph Coveney

Joseph Coveney, Ph.D.
Director, Regulatory Affairs

DIVISION DIRECTOR
PRE-ADVISORY COMMITTEE MEMORANDUM

NDA:	**20,887**
DRUG:	**ACUTEST Kit for the preparation of Technetium Tc99m Apcitide**
INDICATION:	**For the detection of acute venous thrombosis**
CATEGORY:	**1P - Original Submission**
SPONSOR:	**Diatide, Inc.**
SUBMITTED:	**August 20, 1997**
ADVISORY COMMITTEE:	**February 09, 1998**
PREPARED:	**January 20, 1998**
PDUFA DATE:	**February 20, 1998**

/S/ 01/20/98

Dosage Form:	**Reconstituted Kit (radioactive)**
Drug Product:	**^{99m}Tc Apcitide**
Route of Administration:	**Intravenous**
Dose:	**20 mCi ^{99m}Tc with 100 ug apcitide**
Imaging Modality:	**SPECT**

RELATED REVIEWS:

Chemistry - Q. Salako 12/9/97 & 2/13/97
Clinical - J. Zolman - 12/10/97; AE Jones - 12/11/97
Clinical Pharmacology - D. Udo (draft), D. Lee - 02/09/98
Microbiology - B. Uratani 10/3/97
Pharmacology/Toxicology - A. Laniyonu - 01/12/98
Statistics - M. Sobhan - 12/5/97 & 1/20/98
Project Manager - C. Ferre-Hockensmith

BACKGROUND:

Diatide, Inc. has developed a chemically peptide for binding with activated platelets. This property is hypothesized to identify activated platelets that are located on propagating thrombi and, thereby, will identify acute venous thrombosis. The implied (but not systematically studied) clinical utility of such a product is that the ability to distinguish an acute from an older thrombus will help physicians in selecting treatment interventions.

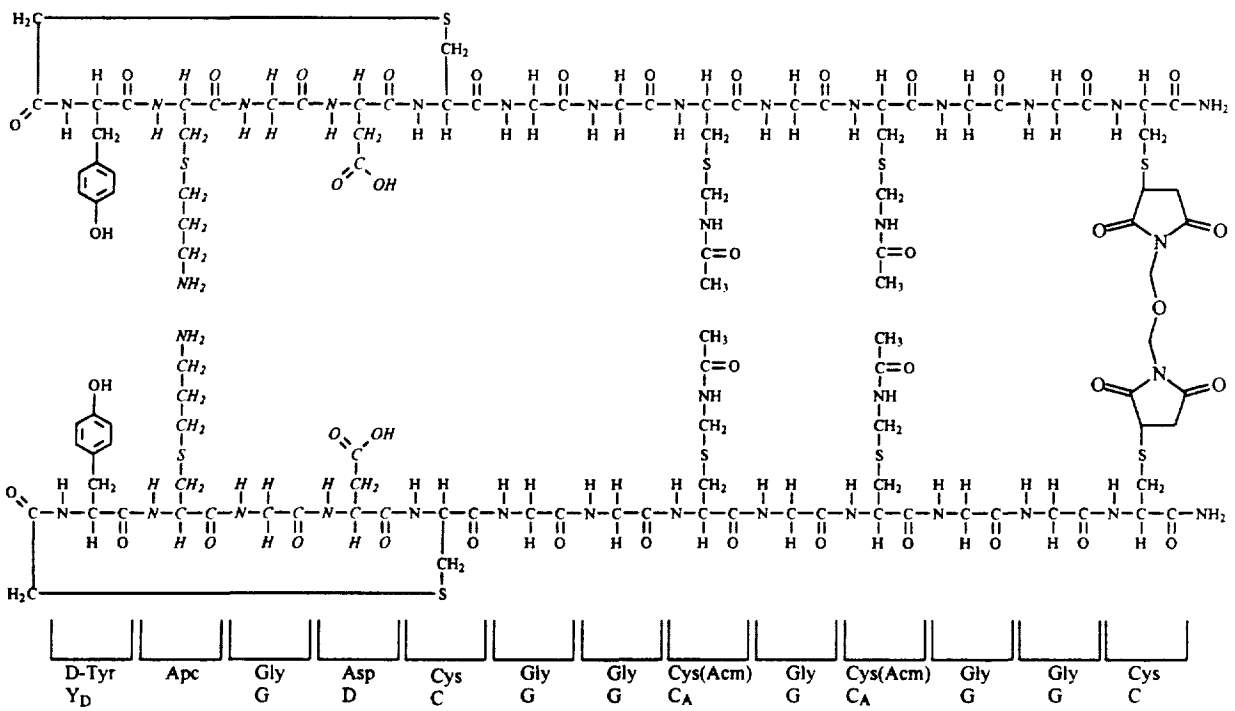
The sponsor's indication as stated in their proposed package insert is that *"Acutest is indicated for the scintigraphic imaging of acute venous thrombosis"*.

A central issue in the overall assessment of this NDA is the documentation of the receptor binding capacity of the ligand, and the fact that the external standard of "truth" to document the presence or absence of an acute venous thrombosis is suboptimal. Also, the method of image analysis may affect the findings of the standard of truth. Therefore, the final assessment of the Acutest data may differ from various approaches to the existing clinical standard.

The clinical and statistical reviewers recommend non-approval because the inconsistent performance of the clinical standard in one of the two pivotal studies. The other reviewing disciplines (chemistry, microbiology, pharmacology-toxicology, and clinical pharmacology-phramcokinetics) recommend either approval or approvable pending labeling revisions and phase 4 commitments. Salient aspects of these recommendations will be addressed in this memorandum.

CHEMISTRY:

Acutest Kit for the preparation of Technetium Tc99m Apcitide is a lyophilized powder that is reconstituted with sodium pertechnetate Tc 99m injection, USP. The molecular formula is $C_{112}H_{162}N_{36}O_{43}S_{10}$; the chemical name is 13,13'-[Oxybis[methylene(2,5,-dioxo-1,3-pyrrolidinediyl)]]bis[N-(mercaptoacetyl)-D-tyrosyl-S-)3-aminopropyl)-L-cycteinylglycyl-L-α-aspartyl-Lcysteinylglycylglycyl-S-[(acetylamino)methyl)-L-cysteinylglycyl-S-[(acetylaminio)methyl}-L-cysteinylglycylglycyl-L-cysteinamide],cyclic (1→5), (1'→5')-bis(sulfide). Apcitide is a sterile solution of a 13 amino acid monomer that is formed during reconstitution. The supplied lyophilized powder contains bibapcitide, a symmetrical dimer of apcitide that is linked by a bis(succinimidomethyl) ether bridge at the C terminal cysteine groups. The structural formulas of bibapcitide and apcitide are shown below.



Other ingredients are bibapcitide trifluoroacetate 100 ug, sodium α-D-glucoheptonate dihydrate 75 mg, tin chloride dihydrate 89 µg, hydrochloric acid , sodium hydroxide

MW= 1525.5 Daltons

The proposed dose of Acutest is 20 mCi. Given the vial volume and physical decay of technetium, this would provide apcitide

Dr. Salako has reviewed the chemistry manufacturing & controls portion of the application and recommends approvable pending correction of several deficiencies. ***These are summarized on page 25 - 30 of his review.*** In brief the deficiencies are for clarifications on the regulatory methods for the final intermediate bulk peptide, the peptide drug product, the 99mTc-P246 drug substance, methods validation and labeling. During team discussions after the primary review was completed, it appears that the amount of fragmented peptides in the injectate is not clear.

The sponsor is clarifying this issues.

Overall I agree with the recommendation of approvable pending resolution of the above issues and those outlined in Dr. Salako's review. At the time of this writing, the reviewer and sponsor are in communication about these issues.

EA- The environmental assessment is adequate for a categorical exclusion on the basis of an expected introduction concentration of

EER - pending at the time of this writing

MICROBIOLOGY:

Acutest is a sterile solution. During the review process, Dr. Uratani identified several issues. These have been resolved and the microbiology portion of the application is recommended for ***approval.*** I accept this recommendation.

PHARMACOLOGY / TOXICOLOGY:

Acutest administers ^{99m}Tc apcitide. The pharmacology studies were submitted to confirm (among other things) the binding of apcitide to the glycoprotein α_2/β_3 receptors of activated platelets, to evaluate the potential platelet inhibitory affect of apcitide and the other peptides in the injected formulation, to evaluate the potential for cross reactive binding to other receptors on inactive platelets, and to the vitronectin receptors of endothelial cells. The toxicology data included special studies of drug interaction with anticoagulants such as aspirin, and heparin.

Dr. Laniyonu has reviewed these data and recommends approvable for pharmacology-toxicology portion of the application I agree with this recommendation. Several pertinent features of this section of the application are discussed in the following paragraphs.

The receptor binding properties of apcitide were documented in animal models and in human *in vitro* studies. Apcitide binds to the α_2/β_3 receptors on activated human platelets[1]. This receptor is used to bind fibrinogen to the platelet. The α_2/β_3 is part of a group of receptors known as integrins. The endothelial lining contains a vitronectin receptor (α_5/β_3) with an identical β_3 chain. As described in Dr. Laniyonu's review pages 8-10, the ratio of binding to the platelet α_2/β_3 versus the vitronectin α_5/β_3 receptor is 1.8/100 ηM. This suggests that apcitide binds preferentially with activated platelets. However, the possibility of cross reaction with the vitronection receptors might affect the interpretation of the images in patients with acute thrombosis and acute phlebitis. Also, percent of binding washed unactivated platelets is 4%; the binding to activated platelets is 10% of the injected dose.

The injected Acutest contains 2 other peptide fragments known as P1007 and P1008. The affect of these fragments and apcitide on platelet aggregation was studied. Platelets normally aggregate in the presence of ADP. In part this aggregation involved the binding of fibrinogen to the α_2/β_3 receptor. If apcitide, P1007 or P1008 are bound to the receptor, then platelet aggregation might be affected. In platelet enriched human blood studies, apcitide, P1007 and P1008 inhibited platelet aggregation. However, the IC_{50} in the injectate is 7 times more than the total injected dose of apcitide and peptide fragments.

Table 1 [(a)]
SELECTED PEPTIDE FRAGMENT CHARACTERISTICS

Fragment	Vial Concentration		% Inhibition of Fibrinogen Binding to GP α_2/β_3 (IC_{50})	% Inhibition of Platelet Aggregation (IC_{50})
	Before Reconstitution	After Reconstitution		
Babapcitide (P280)	≥93 ug	--	≈ 1.8 nM	63 ± 21
Apcitide (P246)	--	21 ug	≈ 1.8 nM	382 ± 108
P1006	≤ 7 ung	--	--	not determined
P1007		64 ug	--	52 ± 2
P1008		15 ug	--	689 ± 143

1) Technetium Tc 99m apcitide binds specifically to washed platelets
2) 77% specific binding to platelets was inhibited by the presence of cold bibapcitide
3) Platelet activation produced an ≈ 3 fold increase in binding

(a) Prepared by Drs. Laniyonu and Salako

[1] In the application and in various reviews uses the nomenclature of GP II/GPIII, and α_2/β_3 are used interchangeably.

As noted in the clinical safety section, platelet function as measured by bleeding time was not studied. In *in vitro* studies, Acutest was not shown to interfere with the anticoagulant function of aspirin or heparin.

The pharmacodynamic affect of Acutest was studied in a dog model of experimentally induced thrombi. (See Dr. Laniyonu's review pages 15-16 for a more complete discussion). In this study imaging was completed with ^{99m}Tc-HMPAO-platelets, ^{99m}Tc-glucoheptonate and Acutest. The ^{99m}Tc-HMPAO-platelets are expected to be avidly incorporated into a developing thrombus. The ^{99m}Tc-glucoheptonate is considered a negative control. Imaging of experimentally induced actively developing thrombi was completed with each agent. The ^{99m}Tc-HMPAO-platelets gave the most positive thrombus identification with images rated as "excellent", the Acutest images were rated as "good", the ^{99m}Tc-glucoheptonate images were the least positive at "none".

Concept assessment: The receptor binding properties of apcitide have been demonstrated as reasonably selective binding to the α_2/β_3 receptor of activated platelets with lesser cross reaction to the vitronectin binding receptor on endothelial cells α_5/β_3. The apcitide and peptides has demonstrated dose response affects on blocking fibrinogen binding to the receptor and, hence inhibits platelet aggregation. The NOEL (no observable effect level) has not been established clearly. And, in some animal models the platelet count decreased at approximately 30 times the MHD. Whether these effects are clinically relevant is not clear from these studies. Drug interaction with aspirin or heparin was not demonstrated at the tested doses.

Elimination is predominately by the kidney, and in animal models elimination is decreased by renal impairment. Hepatobiliary excretion increased in renal dysfunction. Consistent decrease in spleen weight and lymphoid depletion on histopathology; however, clinically identified changes were not demonstrated. Peripheral blood counts varied. Mice appear to be more sensitive

The toxicology studies demonstrated a reasonable safety profile with the notable exception of a decrease in splenic weight noted in all species that were studied in multiple dose models. Splenic weight reduction is often associated with lymphoid depletion. However, clinical manifestations of this were not clear. Also, Dr. Laniyonu raised a question about the potential for gender differences in platelet activity because of published gender differences in platelet function. This was not studied further. Reproductive toxicity studies were waived. Genotoxicity and mutagenicity studies were negative.

PHARMACOKINETICS / PHARMACODYNAMICS:

Drs. David Lee and David Udo reviewed the clinical pharmacology portion of the application. Dr. Udo's review is filed in draft with additional team leader comments from Dr. Lee. Dr. Lee's review should be read first and supplemented with Dr. Udo's. The essence of their reviews concludes that Acutest is approvable with labeling revisions

I agree with this recommendation. The pharmacokinetics parameters are outlined briefly in the following table.

Table 2
SELECTED PHARMACOKINETICS PARAMETERS

Radiation emission	gamma 140.5 kev
^{99m}Tc physical $t_{1/2}$	6.02 hours
$T_{1/2}$	2.0 ± 0.5 hours
Cl_T	1.9 ± 0.7 hours
Elimination Urine Fecal	 ~50% by 2 hours ~75% by 8 hours ~80% by 24 hours ~10% by 24 hours

APPEARS THIS WAY
ON ORIGINAL

CLINICAL - STATISTICAL:

The Acutest NDA clinical database consists of 13 clinical studies of which 2 are submitted to provide "pivotal" data (study # 280-32 A and B). Across all studies, 714 patients were enrolled and 710 were exposed to at least one developmental formulation of Acutest. This included 21 healthy volunteers, 689 patients, 382 men and 328 women. The mean age was 56.7 years . Racial or ethnic group data are available on 604 subjects who received the proposed for market formulation. Of these the representation is 82% Caucasian, 12.7% Black, 2.7% Hispanic, and 2.6% other groups. The following table briefly summarizes the number of subjects who enrolled, received Acutest, completed or dropped for various reasons (the first column). The next group of columns groups the data by phase 1, 2 or both (subtotals) and for all patients (totals). The subdivided columns list the number of subjects evaluated in early development formulations (other) and the formulation proposed for marketing (FPFM).

Table 3 [a]
NUMBER OF SUBJECTS ENROLLED IN THE Acutest CLINICAL STUDIES OF NDA 20,877

	Phase 1		Phase 2		Subtotals		TOTALS
	Other[b]	FPFM ©	Other	FPFM	Other	FPFM	ALL
Enrolled	10	20	68	616	78	636	714
Exposed	10	20	68	612	78	632	710
Completed	10	18	68	575	78	593	671
Dropped	0	2	0	41	0	43	43
Adverse event	0	0	0	1	0	1	1
Withdrew	0	0	0	4	0	4	4
OTHER	0	1	0	36	0	37	37
Before Acutest	0	0	0	4	0	4	4
After Acutest	0	1	0	32	0	33	33
Missing	0	1	0	1	0	2	2

(a) Adapted from sponsor table 1, facsimile of 1/12/98
(b) Other = early development formulations
© FPFM = formulation proposed for market

(Continued)

APPEARS THIS WAY
ON ORIGINAL

Table 4 [a]
SELECTED CHARACTERISTICS OF THE Acutest CLINICAL STUDIES IN NDA 20,887

Phase	Study	N [b]	Purpose	Image Blinding	Peptide	mCi
1	280-10	10	PK, radiation dosimetry	--	100	10
1	280-11	20	"	--	100	20
2	280-20	10 16 5	Dose finding-known thrombosis	Blind read	250 250 250	10 20 30
2	280-22	28	Dose finding	Blind read	20, 50, 100*	5, 10, 20*
2	280-00	9	Known venous thrombosis	--	125 - 250	10
2	280-01	26	Brain tumor	--	230	25
Totals of early formulations		78				
Ph2	280-21	30	Variety of disorders	--	<100	20
Ph2	280-23	14	Other Disorder	--	100	~20
ph2/3	280- 30 A & B	135	Acutest vs Doppler	Blinded control Open Acutest	<100	20
ph 2	280-31	22	Exploratory	--	<100	20
Pivotal	**280-32A**	**133**	**Acutest vs Venography**	**Blinded Acutest & control**	**70-100**	**20**
Pivotal	**280-32B**	**145**	**Acutest vs Venography**	**Blinded Acutest & control**	**70 -100**	**20**
safety	280-33	107	Efficacy and immunogenicity	---	70 - 100	20
Total Proposed for Market Formulation		636				
NDA Total		714				

(a) Adapted from sponsor's submission and reviews
(b) Number enrolled

APPEARS THIS WAY
ON ORIGINAL

Phase 1 and 2 studies provided the basis of the pharmacokinetics data discussed in the preceding section and the dose selection. The dose selection studies included variations in the amount of peptide and the amount of radioactivity. The selected amount of radioactivity (20 mCi) is

consistent with the technical adequacy of most SPECT imaging. The amount of peptide in the study used for dose selection (protocol 280-22) ranged from 20 to 100. Higher peptide doses has been studied for other indications (e.g., brain tumor). In this study there was a weak trend toward a correlation of the higher peptide dose with venographic findings. A larger sample size is needed to confirm the findings. Drs. Jones and Zolman note that phase 2 did not establish the optimal imaging time, however, in the phase 3 studies, several time points were evaluated.

Data across a variety of conditions was variable. Particularly in study # 280-21 of patients with a number of disorders that might be associated with acute thrombosis, the Acutest findings seemed to identify thrombi in patients with TIA and venous graphs but less so in patients with a history of pulmonary emboli. Study P280-23 evaluated patients with carotid artery thrombi, the results are preliminary. Overall in the phase 2 studies, the agreement of Acutest with either venography or doppler was roughly 60%.

Three phase 3 studies were conducted. Two of these were controlled by venography and one by ultrasound. A critical feature of this NDA is how to interpret the statistical results in reference to the imaging control clinical standard. Acutest is proposed to produce an image associated with acute thrombi. The clinical standard for thrombosis is an iodinated contrast venogram. It identifies the anatomic presence of a thrombus or venous narrowing from plaque formation. It can suggest the age of a clot by the presence or absence of collateral circulation. It can not determine whether the thrombus or part of it is new or old. Also, ultrasound Doppler is frequently used and is considered by some to be comparable to contrast venography. However, it has limited effectiveness in identifying thrombi in the calf or pelvis. It can not determine the age of the clot. Another uncommonly used and often unsuccessful diagnostic test is ^{125}I-fibrinogen. This is not marketed currently.

At the point of this discussion, a phase 3 trial with Doppler was underway. Diatide chose to stop that study and start new ones with the venogram control. All 3 studies are in the NDA. The venogram controlled studies were submitted with a full blinded read of all images. The Doppler controlled study had a blinded read of the Doppler control but an open label read of the Acutest images.

Drs Zolman and Sobhan reviewed the clinical and statistical data from the 2 venogram controlled studies and recommend non-approval of the application because of the lack of statistical significance in the primary outcome measure (agreement with contrast venography with a 60% lower confidence bound). These issues are discussed below.

The clinical trial design of the multicenter and multinational 280-32 A & B protocol is identical. The studies were nonrandomized enrollment, open label, randomized blinded read, within patient evaluations of the ability of Acutest to detect acute venous thrombosis identified by contrast venography. All eligible patients were adults had symptoms of the onset of acute thrombosis within 10 days of study entry. These symptoms included pain or tenderness, swelling, increased warmth, erythema, or a palpable cord.

Patients received a contrast venogram and Acutest imaging within 10 days of the onset of clinical symptoms that suggested acute venous thrombosis or within 10 days of a surgical procedure that is associated with the development of an acute venous thrombosis. The Acutest images were taken within 36 hours before or after contrast venography. All imaging began and was completed within 36 hours of either imaging study. Also, patients could being treatment before imaging. Acutest images were taken at 10, 60 and 120-180 minutes after injection.

The primary outcome measure is the agreement of the blinded Acutest and blinded Contrast venography results. The results were considered to agree if there was one region or contiguous region in common with the contrast venogram.

Secondary outcome measures included sensitivity and specificity of the blinded reads, and the agreement with the unblinded read. The raw data for Acutest was derived from blinded reader case report form questions of 1) side of involvement - right or left, 2) intensity of uptake - slight, moderate or intense, 3) shape of the lesion - circular, linear or irregular, 3) extent of vessel involvement - <1/4, 1/4 to < ½ , ½ to < 3/4, or >3/4. These measures were scored for the iliac, thigh, knee or calf. In single or full sets, a positive image had "asymmetrical uptake (with or without superimposed diffuse uptake in contrast enhanced images". "Asymmetry must be present in both anterior and posterior projections" and "if asymmetry appears only after extreme contrast enhancement", it was to be called "positive there is also a diffuse asymmetry, negative if not diffuse asymmetry". The readings were for deep veins only. Superficial vein thrombi were not to be called positive. Intermediate = a diagnosis could not be made.

The prospectively planned efficacy endpoints was that Acutest image results would have a 60% agreement with the contrast venography results. This would be true, regardless of a positive or negative result on the venogram. As discussed in detail in Dr. Sobhan's statistical review, the results of the 2 pivotal studies are inconsistent and ranged between approximately agreement. The sponsor is aware of this inconsistency and performed several analyses after the results of the planned analysis were known.

Blinded image read protocols were different for the Acutest and contrast venograms. For Acutest two blinded reading sessions occurred. One was planned in the protocol and one was not. The per-protocol blinded read was completed by 3 independent readers who did not known the patient information, the institution or the enrollment criteria. The images from all times after injection were randomized. The second blinded read by a different independent set of readers evaluated the data in the same way except the images were first read by separate times and then in a combined patient set. For read 1 and read 2, the aggregate findings were reported as the mathematical majority. The results of all 6 readers were submitted. The statistician finds the methods for read 1 and read 2 as acceptable.

For contrast venography there were two blinded reads. The first blinded (planned by the protocol) was conducted by radiologists who were not involved in any aspect of the clinical trial, and did not have patient information. The "truth" was determined by the majority result of the independent interpretations. The second blinded read (termed the Hamilton read) occurred after

the results of the planned analyses were known to the sponsor. This Hamilton read was made by 3 independent readers who did not know the Acutest results. After the blinded reading was completed and scored, if there was disagreement, then the 3 readers met to reach an aggregate consensus standard of truth.

A final onsite clinical diagnosis was determined by chart summary diagnosis.

A summary of the key results of the different Acutest and Contrast Venography reading interpretations is listed in table 4. The left hand column contains the different reading methods, the middle group of columns presents the results of study A. The right hand group of columns lists the results for study B. The table is further subdivided into the percentage of positive and negative results for the diagnosis of acute thrombosis. The row under each study contains the words "yes, no, ?". This refers to whether the image is positive, negative or indeterminate for acute thrombosis. The next table subdivision presents the Acutest agreement with the different contrast venography reading methods (CV). The next subdivision presents the Acutest and CV method agreements with the final clinical diagnosis.

(Continued)

APPEARS THIS WAY
ON ORIGINAL

Table 5 [a]
SUMMARY OF SELECTED RESULTS OF Acutest AND CONTRAST VENOGRAPHY INTERPRETATIONS, NDA 20,877

	Study 280-32 A N = 114			Study 280-32 B N = 123		
PERCENTAGE OF POSITIVE AND NEGATIVE INTERPRETATIONS OF ACUTE OR CHRONIC THROMBOSIS						
Acutest	Yes	No	?[b]	Yes	No	?
Read 1 Blinded			--			--
Read 2 Blinded			--			--
CONTRAST VENOGRAM (CV)						
Onsite Open	44 (38%)	71 (62%)	--	66 (54%)	57 (46%)	--
Per protocol Blinded (Majority)	51 (45%)	63 (55%)	--	101 (82%)	22 (18%)	--
Hamilton Blinded (Consensus)	24 (21%)	86 (75%)	4 (4%)	40 (33%)	80 (65%)	3(2%)
FINAL CLINICAL DIAGNOSIS						
	45 (39%)	70 (61%)	--	67 (54%)	56 (45%)	--
Acutest AGREEMENT WITH CV READING METHODS (PRIMARY OUTCOME MEASURE)						
Institutional Open Read CI interval includes 60%	3/6 readers			4/6 readers		
Per protocol Blinded CI interval includes 60%	3/6 blinded readers			6/6 blinded readers.		
Hamilton Blinded CI interval includes 60%	3/6 blinded readers			2/6 blinded readers		
Acutest OR VENOGRAM AGREEMENT WITH THE FINAL CLINICAL DIAGNOSIS						
Acutest	94/115 (70%)			78/123 (63%)		
Onsite Open Read	94/115 (70%)			86/123 (69%)		
Per protocol Blinded	80/115 (59%)			76/123 (61%)		
Hamilton Blinded	89/113 (79%)			91/123 (74%)		

(a) Adapted from sponsor's submission; (b) "?" = Indeterminate, © range for 3 blinded readers; see Dr. Sobhan's review tables that list the results for each blinded reader

The sponsor felt that one reason for the failure to confirm the primary outcome variable is the failure of the venography reads. The sponsor compared the blinded control results of two methods of blindly reading the venograms; these ranged for the different readers. The combined rate is 56.1%. A little better than arbitrary chance.

The Hamilton read did not make a difference in the marginal acceptance of study A. But, it would change the results of study B. (But the same 3 readers read both study A and B. Therefore, the consensus read is not independent. Retrospectively one reader could be selected for each study. Since all 3 reject the null in study B, this would still change the results of B).

Sponsor's interpretations: Diatide submitted a series of assessments to determine which is the most appropriate blinded assessment of the venogram. Literature references were cited for the over interpretation of venograms also. The sponsor asserts that the clinical onsite read is the most realistic for a given patient. Given the fact that the two methods of blinded read gave somewhat different results, the sponsor asserts that the blinded read that is most closely aligned with the unblinded read is correct. That read is the Hamilton. Therefore, for overall interpretation of the clinical trials, the appropriateness of accepting a post hoc blinded read must be considered.

SAFETY

General safety of Acutest was discussed in Drs. Jones, Zolman and Sobhan's review. Overall, Acutest appears to be reasonably safe and is associated with at least one adverse event in approximately 6% of the 632 subjects were exposed to the Acutest formulation proposed for market (see demographics table on page 7). Deaths were not reported in this study population. There was one serious event; hypotension within 10 minutes of injection. This patient responded to fluid administration. The sponsor provided adverse events by phase 2 and 3 groupings. This excluded a few patients who received the proposed for market formulation that were studied in phase 1. The sponsor is requested to revise the package insert to reflect all patients who received the proposed for market formulation. The most frequent event was pain (either in association with acute venous thrombosis or otherwise). Pain was reported in 10 (1.6%) of the patients. The next most frequent event was headache in 5 (0.8%) of the patients, hypertension in 4 (0.6%) of the patients, and fever 5 (0.5%) of the patients.

The limitation of the safety database is the number of subjects who were monitored for prolonged time periods. Of the 632 subjects who received the new formulation, only 169 were monitored at 24 hours. Diatide's rationale for the limited monitoring is that in phase 1 & 2, adverse events were not noted after 3 hours and the drug is 905 eliminated by 24 hours. Therefore, longer monitoring was not done in phase 3.

Preclinical studies of Acutest noted the ability of the peptide to inhibit fibrinogen binding to activated platelets. Possible potential clinical manifestations include increased bleeding potential. Clinical studies of platelet function (such as bleeding time) were not conducted.

Acutest is a peptide. As such it is apt to stimulate allergic manifestations. Immunogenicity was evaluated in a special safety study (P280-33) of 32 patients. The potential of nonspecific antibody formation was assessed by measuring specific immunoglobulin IG responses to apcitide and a peptide fragment P1007. The patients received one dose of Acutest. The IgG levels were measured at baseline and 3 weeks later. The mean levels were similar and within 2 standard deviations of the mean. The study did not evaluate other assessments of immune function such as complement, immune complexes or lymphokines. Repeat dose studies for hypersensitivity were not done.

DSI - one is pending at the time of this writing; the other clinical sites are acceptable.

Safety assessment: The NDA database beyond 3 hours is limited, bleeding time was not performed and the hypersensitivity assessment is preliminary.

ASSESSMENT

Recommendations accepted as preliminary pending the MIDAC committee meeting.
Chemistry - approvable pending resolution of drug substance and other issues faxed to the sponsor
Microbiology - approval
Pharmacology /Toxicology - approvable with labeling
Clinical Pharmacology - approvable with labeling
Clinical/Statistics - not approved
Clinical Safety - not approved

Final letter is pending the discussion and consideration of the advisory committee comments and recommendations.

In the interim, the chemistry issues have been discussed with the sponsor. Labeling and a letter are being drafted and are subject to revision post advisory committee meeting.

INTERIM RECOMMENDATION: Non-approval pending MIDAC discussion of the following items.

Diatide, Inc.

9 Delta Drive • Londonderry, New Hampshire 03053
(603) 437-8970 • FAX(603) 437-8977

October 24, 1997

Division of Medical Imaging and
Radiopharmaceutical Drug Products (HFD-160)
Center for Drug Evaluation and Research
U. S. Food and Drug Administration
Parklawn Building, Room 18B-08
5600 Fishers Lane
Rockville, Maryland 20857

Re: NDA 20,887
Kit for the Preparation of Technetium Tc 99m Apcitide

APPEARS THIS WAY
ON ORIGINAL

Dear Sir or Madam:

Diatide, Inc., hereby amends the NDA referenced above to claim a categorical exclusion from the requirements to include an Environmental Assessment in accordance with 21 CFR 25.15 (d), as published in the *Federal Register*, Vol. 62, No. 145, Pages 40,569 - 600, July 29, 1997.

NDA 20,887 complies with the categorical exclusion criteria of 21 CFR 25.31 (b) inasmuch as the active moeity's entry introduction concentration into the aquatic enviroment will be This value has been calculated in accordance with the method specified in *Guidance for Industry For the Submission of an Environmental Assessment in Human Drug Applications and Supplements*, November 1995, Pages 13-14. The calculations already appear in the original NDA, in Volume 1.7, Pages 199-200.

To the best of the applicant's knowledge, no extraordinary circumstances exist as defined in 21 CFR 25.21.

The applicant waives the claim for categorical exclusion if a finding of no significant impact has been signed on or before August 28, 1997, for this NDA.

Sincerely,

APPEARS THIS WAY
ON ORIGINAL

J. Kris Piper,
Senior Director, Regulatory Affairs and Quality Assurance

Niatide, Inc.

9 Delta Drive • Londonderry, New Hampshire 03053
(603) 437-8970 • FAX (603) 437-8977

November 7, 1997

Division of Medical Imaging and Radiopharmaceutical Drug Products (HFD-160)
Center for Drug Evaluation and Research
Food & Drug Administration
Parklawn Building, Room 18B-08
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20887
Amendment

APPEARS THIS WAY
ON ORIGINAL

Dear Sir or Madam:

Please find enclosed our response to microbiology comments we received on October 24, 1997.

The reviewer's comments are presented in bold type followed by our response.

Please contact me if you need clarification or additional information.

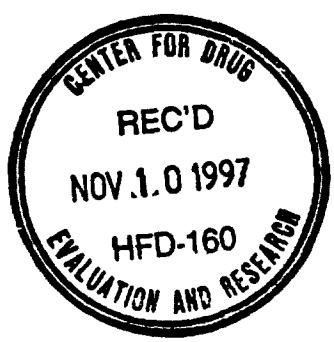
Sincerely,

J. Kris Piper
Senior Director Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

JKP/slb

enclosures



DIVISION OF MEDICAL IMAGING AND RADIOPHARMACEUTICAL DRUG PRODUCTS

HFD-160

NDA: **20-887**
NAME: **AcuTect**
APPLICANT: **Diatide, Inc.**
DATE RECEIVED: **16 Mar 1998**
REVIEW COMPLETED: **08 Jun 1998**

This document contains the sponsor's proposals for studies and protocols in response to the requests and comments that were in the approvable letter of 20 February 1998. This review identifies the FDA requests in the numerical order listed in this submission and the adequacy of the request is assessed.

1. Submit the criteria for the Hamilton blinded reading of contrast venograms that were presented by your consultant, Dr. Ginsberg, at the February 9, 1998 Medical Imaging Advisory Committee (MIDAC) meeting.

Comment: The sponsor's response is located in Appendix 1. It does not contain a copy of the sponsor's original protocol for the venography reading that Dr. Ginsberg would be expected to follow prior to beginning the retrospective readings of the venograms. The package insert refers to two methods the latter being the Hamilton (Ginsberg's) read which should have a protocol. It should identify the venogram characteristics that would denote thrombosis, its location and extent, how readings would be conducted, e.g., independent readers, with or without consensus and how adjudication would be conducted whether or not in the presence of the reader(s). The example of blank case report forms (CRFs) was not provided. Criteria for designating venograms inadequate and how to handle such cases are not provided.

2. Clarify the discrepancy in the amount of apcitide binding to the vitronectin receptors. At the MIDAC meeting, your slides gave 1000 nanomolars for 50% inhibitory concentration. The submitted study states 100nM.

Comment: The sponsor's response is adequate, however I defer the assessment of the adequacy of this response to the appropriate review discipline.

3. Submit patient narratives for the following laboratory changes that were above the upper limit of normal in study 280-33. Patient 20-1 for aminolevulinic acid and alanine aminotransferase; patient 5-2, 7-3, and 8-3 for gamma glutamyl transferase; patient 21-1 alanine aminotransferase and alkaline phosphatase; patient 10-1 alkaline phosphatase.

Comment: A response has been provided for all of the patients identified. Patient 01-20 experienced a transition from normal to abnormal enzyme levels within three hours following Acutect. The enzyme levels remained elevated at 24 hours post dose and were not further followed. There is no evidence provided to support the investigator's claim that this was not due to Acutect. In fact it is noted that there was hepatomegaly

and ascites noted following the Acutect procedure. For patient 02-05: I agree that the slight rise of GGT was not clinically significant however it did occur within three hours following the Acutect dose and did not return to normal by 24 hours. Patient 03-007 also experienced a small rise in GGT into a low abnormal value noted at 24 hours, presumably due to Acutect. Patient 03-08 was similarly noted to have a low abnormal GGT at three and 24 hours again following administration of Acutect. Patients 01-21 and 01-10 had disease that would elevate the AST and alkaline phosphatase (patient 01-21) and alkaline phosphatase (patient 01-10) respectively at the baseline assessments of these enzymes but there is no evidence to eliminate the possibility that the elevations in these enzymes noted following Acutect were not due to this drug. I conclude that the enzyme elevations were Acutect related in all of these patients .

4. Submit revised draft labeling identical in content to the enclosed draft dated February 19, 1998. If additional information relating to the safety and effectiveness of this drug becomes available, revision of the labeling may be required.

The sponsor has complied with this request and this reviewer has the following concerns:
Indications and Usage: The last words should be '

Warnings: The last sentence of the first paragraph should be changed to read as follows:

Precautions: The second paragraph regarding ' ' should be altered to read: The sponsor's Technical Report No. R0.001, Update 1 does not provide substantial evidence to eliminate the possibility that AcuTect is immunogenic. In addition there should be mention of abnormal liver enzyme tests following the use of AcuTect. A statement such as the following may be considered:

Laboratory Tests: The following statement should also be included under the Precautions section of the package insert:

I recommend that the word

Phase 4 Commitments:

2 PAGES REDACTED

CONTAINED TRADE SECRETS and/or CONFIDENTIAL/ COMMERCIAL INFORMATION

During recent inspections of the manufacturing facilities for your NDA, a number of deficiencies were noted and conveyed to you or your suppliers by the inspector. Satisfactory inspections will be required before this application may be approved.

Comment: The reviewing chemist will respond to this commitment. The final response is intended to be provided by the sponsor to meet the required CGMPs.

Under 21 CFR 314.50(d)(vi)(b), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. **Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission.**

Comment: The sponsor has provided an adequate response which is supplied in Attachment 7.

2. **Retabulation of drop-outs with new drop-outs identified, As appropriate, these new drop-outs should be discussed.**
3. **Details of any significant changes or findings.**
4. **A summary of worldwide experience on the safety of this drug.**
5. **Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.**
6. **English translations of any approved foreign labeling.**
7. **Information suggesting a substantial difference in the rate of occurrence of common but less serious adverse events.**

Comment: All of the above requests made by FDA to the sponsor under 21 CFR 314.50(d)(5)(vi)(b), were answered briefly and adequately with worldwide safety experience listed in tables 1-4 Attachment 7. Table 4 provides the Summary Of The Reported Adverse Events updated from the table submitted January 13, 1998 with one change in the updated table where "hypotension" numbers were altered.

Additional patent information.

The sponsor provided an update of patent information as requested. This is located in Attachment 8 and provides the patent number US 5,670,133; the expiration date, 9/23/2114; type of patent, drug, drug product; and the name of the patent owner,

Conclusion:

The sponsor has responded to all requests made in the approvable letter dated 20 February 1998. There are some requests and recommendations to the sponsor that follow.

Recommendations:

1) The alterations in liver enzymes that were recorded at three and 24 hours following the administration of AcuTect were not followed until return to abnormal or otherwise adequately evaluated at the time of their detection. There is no evidence to support the possibility that they were not due to AcuTect. Please propose a further evaluation of abnormal liver enzymes occurring following the administration of AcuTect. As it remains, it is necessary to provide comment in the Precautions section of the labeling.

2) The following changes in the package insert are recommended:
Indications and Usage:

Warnings: The last sentence of the first paragraph should be changed to read as follows:

Precautions: The second paragraph regarding should be altered to read: The sponsor's Technical Report No. R0.001, Update 1 (page 000037, at the end of Attachment 3) does not provide substantial evidence to eliminate the possibility that AcuTect is immunogenic. In addition there should be mention of abnormal liver enzyme tests following the use of AcuTect. A statement such as the following may be considered:

Laboratory Tests: The following statement should also be included under the Precautions section of the package insert:

To The Sponsor:

1) Your response to item 1. Page 000002 is incomplete please send the protocol and the blank case report forms. The package insert refers to two methods the latter being the Hamilton (Ginsberg's) read which should have a protocol. It should identify the venogram characteristics that would denote thrombosis, its location and extent, how readings would be conducted, e.g., independent readers, with or without consensus and how adjudication would be conducted whether or not in the presence of the reader(s). An example of blank case report forms (CRFs) was not provided. Criteria for designating venograms inadequate and how to handle such cases are not provided.

3) In the proposed study of normal human volunteers to evaluate the effect of AcuTect on prolonging clinical bleeding time, please consider the suggestion that labeled AcuTect be used after it has been allowed to radiodecay. Your proposal to use unlabeled AcuTect otherwise is less exact in paralleling the clinical situation.

4) In regard to the issue of AcuTect reaching fully occluded (thrombosed) veins your explanation was based on observation with no accompanying data and it is therefor hypothetical. Your proposal for a non-clinical study to explore this issue is of help. Please consider comparing your AcuTect image in a few representative occlusive thrombosis models with an image derived from a similar radioactive dose of sodium pertechnetate. There may be a component of inflammation that is influencing the appearance of the AcuTect image and it would be helpful to know how the thrombotic component of the AcuTect image differs in appearance from the inflammatory component of acute phlebitis.

Items 1, 2, and 4 (above) were discussed in a telephone call to Diatide Inc., with Mr. K. Piper, June 12, 1998 made by C. Ferre-Hockensmith and this reviewer.

CC:
NDA 20-887
CSO: C. Ferre-Hockensmith
M.O.: J. Zolman M.D.

/S/ June 12, 1998
A. E. Jones M.D.
Clinical Team Leader, HFD-160

addendum: Sponsor submitted revised ADE monitoring card. It is improved but does not have a space for CO-START which would be helpful. It is as complete as is reasonable.
/S/ 8/20/98

DIVISION OF MEDICAL IMAGING AND RADIOPHARMACEUTICAL DRUG PRODUCTS
HFD-160

CLINICAL TEAM LEADER'S SECONDARY REVIEW

NDA: 20-887

Drug Substance: Kit for the Preparation of Technetium Tc99m Apcitide
Dosage Form: Reconstituted kit
Drug Product: ^{99m}Tc Apcitide
Proposed Trade Name: Acutect™
Route of Administration: intravenous (iv)
Proposed Dose: 20 mCi and 100 ug (approximately)
Proposed Use: Scintigraphic imaging of acute venous thrombosis
Classification: Priority
Applicant: Diatide Inc.
Date Received: 25 August 1997
Review Completed: 11 December 1997
Related Reviews:
Chemistry: Q. Salako
Clinical: J. Zolman
Clinical Pharmacology and Biopharmaceutics: D. Udo
Microbiology: B. Uratani
Pharmacology/Toxicology: A. Laniyonu
Statistics: M.Sobhan
Project Manager: C. Ferre-Hockensmith

BACKGROUND:
The following information on thrombophlebitis and deep-vein thrombosis is derived from Cecil Textbook of Medicine 19th edition 1992 published by W. B. Saunders Company, pages 364-366.

'Thrombophlebitis' is used to refer to a venous blood clot, i.e., thrombus, in the presence of inflammation of the venous wall. Venous thrombosis in the absence of inflammation is termed phlebothrombosis. Superficial thromboplebitis does not cause embolic complications however, thrombophlebitis of the deep veins of the lower extremities, i.e., thighs, knees, and calves is the source of 90% of pulmonary emboli.

The pathology involves inflammation of the venous wall with a thrombus consisting of mostly red blood cells (rbc)and a few platelets and fibrin. The thrombus is attached to the venous wall and propagates in the direction of blood flow with the proximal end floating free in the venous lumen. Thus the thrombus may be long for example originating at the venous wall of the calf and

extend to the portion of the vein that passes through the knee. The free tail of the thrombus may break off and flow to the lungs to create a pulmonary embolus.

The applicant claims that Acutect "^{99m}Tc apcitide is a radiolabeled peptide that avidly binds to the GPIIb/IIIa receptor on activated platelets which are incorporated into active clot". The gamma photon energy of ^{99m}Tc provides optimal imaging characteristics for this radiopharmaceutical. This NDA is intended to provide evidence that ^{99m}Tc apcitide is safe and effective in the detection of acute venous thrombosis.

Existing diagnostic tests for the detection of venous thrombosis, may provide uncertain information or may be painful and have associated risk. X-ray contrast venography (CV) is one of the most accurate methods of diagnosing deep venous thrombosis and is considered a "gold standard". It was used as a standard of verification of venous thrombosis in the two pivotal efficacy trials (280-32A and 280-32B) reported in this NDA. The test requires the iv injection of an iodinated contrast medium to define the venous lumen which has been previously emptied by gravity. The finding of a discrete loss of the venous lumen demonstrated by the absence of contrast medium, is indicative of the presence of venous thrombosis. This test is painful and may induce phlebitis and thrombosis.

Acutect is intended to localize active thrombosis, a pathophysiological (functional) event, while CV localizes altered venous anatomy.

Other tests for the presence of venous thrombosis are radionuclide venography and radioisotope-labeled fibrinogen. Both of these tests are less certain in the diagnosis than is the CV. Ultrasonography and "Duplex" ultrasonography (with color-flow doppler) are very useful for the detection of thrombosis above the knee with color flow doppler being almost as reliable as CV.

About a third of patients over 40 years of age who are post operative or have had a recent myocardial infarction, experience deep vein thrombosis. The occurrence of pulmonary embolism and death or disability associated with thrombophlebitis create an urgent need for a better and earlier way to detect this disorder. This application was considered to have a priority for this reason.

Phase 3 Studies: (280-32A and 280-32B)
These two pivotal efficacy trials were prospe~~ctiv~~e, single dose, within-patient (Acutect and CV)studies designed to assess efficacy and vital signs and adverse events. A third study, 280-33, multi center, open label, with-in patient evaluation of patients at risk for venous thrombosis (VT), was conducted to evaluate the safety of Acutect (Vol.63/110). Efficacy data consisted of the institutional diagnosis based on CV and/or ultrasound comparison with Acutect in an unblinded approach. There were 109 patients enrolled and 86 evaluable for efficacy. The efficacy data was not used to support this NDA. There were 30 patients studied for the presence of antibody formation by using an ELISA assay of a serum sample collected approximately 3 weeks after the Acutect dose.

Objectives: The efficacy trials were to detect and localize acute venous thrombosis by gamma scintigraphy and to confirm the finding by contrast venography (CV) as well as to assess the safety of "single venous administrations of 99mTc P280 in patients."(sponsor)
Comment: The standard of comparison was agreed upon by the agency and the sponsor, however it should be noted that the standard of contrast venography is an anatomic observational endpoint whereas Acutect is dependent on the observation of a physiologic (peptide receptor localization) endpoint. Also, the study is limited to "single" venous administrations thereby not evaluating the safety or efficacy of repeat peptide (Acutect) doses.

Patients:
The protocol called for enrolling 130 patients in each of the two Phase 3 studies (280-32A and B) who were 18 years of age or older; who provided informed consent and who were within 10 days of onset of signs and symptoms of thrombophlebitis.
Comment: The protocol did not exclude patients who were under therapy for thrombphlebitis. Thus many patients were treated with heparin at the time of receiving Acutect which underscored the acute nature of their clinical situation.

Dose:
Acutect: 100ug peptide and 20mCi of ^{99m}Tc iv.
The dose used in the Phase 3 studies was selected from the Phase 2 Study, 280-22, a prospective study where data was obtained in 27 subjects employing three doses of radioactivity (5, 10 or 20mCi) and three doses of peptide (20, 50 or 100μg). The sponsor chose to conduct the Phase 3 pivotal studies with the maximum dose of radioactivity and peptide.
Comment: In the prospective dose determination trial there was very little difference in the images between the three

radioactive doses. The reason for the choice of the higher dose of radioactivity was not explained but is probably technical in nature as image quality is maximized as the count rate density in the image is increased. The sample size is small and a statistically meaningful dose determination could not be developed. The choice of dose is not supported by adequate study data.

Imaging: The Phase 3 protocols (280-32A and B)called for the use of a large field of view (LFOV) camera with a parallel hole high resolution collimator to collect images in a 128 x 128 matrix. The minimum counts to be obtained were 300 to 500K for the calves and 750K for thighs and for the pelvis/abdomen 1000K. Imaging was conducted at 10, 60 and 120 to 180 minutes following the dose. The CV study was obtained either before or after the Acutect study.
The imaging feature that would indicate the presence of thrombus was "focal uptake in the vasculature that is greater than either the corresponding contralateral region or surrounding ipsilateral regions or focal uptake that intensifies with time" (sponsor). Nine vascular regions were chosen (left and right calves, knee, thighs, iliacs and inferior vena cava) to be graded for thrombus as negative, indeterminate or positive.
Comment: There was no optimal imaging time established in the Phase 2 studies thus three imaging times were provided in the Phase 3 study. There was the possibility that an active process of clot formation might be demonstrable in the Phase 3 studies by collecting successive timed images. The protocol did not call for such an evaluation.
There was no prospective consideration given to distinguishing localization of Acutect within the phlebitis as opposed to the thrombus.

Safety: The monitoring of vital signs and adverse events was planned with proper case report forms for safety data entry. The monitoring times were 10, 30, 90 and 180 minutes.
Comment: The safety monitoring time for adverse events is too short.

Statistical Plan: This was amended October 21, 1996 defining six reasons for "removal of patients from therapy or assessment"(sponsor), blinding procedures for evaluating Acutect images, primary efficacy variables, and statistical assessment of efficacy plus several other issues.
"The primary indicators of efficacy were the patient-based rates of agreement of each blinded reader's Technetium Tc 99m P280 results with the true diagnosis based on the blinded reads of the contrast venograms"(sponsor).

The statistical efficacy assessment stipulated that "the results were required to support a minimum acceptable ~~agree~~ement rate of 60%. The binomial distribution was to be used to test the null hypothesis—if the lower bound of the one-sided 95% confidence interval for the agreement rate was at least 0.60 then the null hypothesis was to be rejected".

Issues raised by other reviewers that have clinical significance:

Clinical Pharmacology and Biopharmaceutics:
The reviewer, David Udo, made the following observations in his review:
During the preparation of the kit to produce Acutect several peptides are formed denoted as ^{99m}Tc apcitide, P1008 and P1007, and are present in the final formulation in the ratio 20:15:65 respectively. Thus of the 100μg dose there are 20μg that are radiolabeled with ^{99m}Tc to actively bind to platelet receptors.

Following iv injection the kinetics (based on blood data for normals during a 4 hour period post dose) are not influenced by age or gender, the biologic half life is 2.56 hours, plasma protein binding is about 76% with biliary and urinary excretion being 10% and 80% respectively in the first 24 hours. There was evidence of entero-hepatic cycling. The site of the metabolism of the radioactive peptide was not determined. No studies were conducted to assess the metabolism, biodistribution and elimination of Acutect in patients with impaired renal function. Pediatric and geriatric studies were not performed.
Comment: There were no quantitative data to support the sponsor's claim that drug-drug interactions did not occur with warfarin, coumadin, or acetylsalicylic acid. In the Phase 3 studies, patients were treated with these drugs and the possible clinical effects on Acutect were not observed or evaluated.

Radiation Dosimetry: The biodistribution and kinetics of the radiolabeled drug and its metabolites were evaluated for whole body, lung, heart, spleen, breast, kidneys, urinary bladder, brain, and gallbladder. The reported data collection intervals are 10 minutes, 4 and 24 hours. Camera data was collected at 10 minutes, 1, 2, 4 and 22 to 24 hours after injection. The liver contained approximately 1.0% of the radioactive dose at 24 hours and in the entire abdomen there was 2.8% at 24 hours.
Comment: It was reported (Vol. 28, p276) that half of the injected radioactive dose appeared in the urine at 2 hours and three-quarters by 8 hours; 80% underwent urinary excretion by the first day. Organ radiation dosimetry values were tabulated for the package insert. They are low and are not a safety concern.

Pharmacology and Toxicology:

The reviewer, Adebayou Laniyonu, noted that the glycoprotein receptor 11b/111a (GP11b/111a) is present on both platelets and endothelial cell surfaces. The sponsor indicated that platelets must become activated before the receptor can bind fibrinogen and therefore a radiolabeled binding peptide that binds to the GP11b/111a receptor might localize a thrombus. To further characterize the receptor binding peptide, the sponsor did an in vitro study of Acutect and platelet inhibition and found that all the peptides (primarily P1007 and P1008) associated with Acutect inhibited platelet aggregation. The reviewer raised a clinical concern whether repeated doses of peptide within a short period of time might reduce platelet function. The sponsor also conducted an in vitro study of the effect of Aspirin or heparin in relation to the platelet inhibitory effects of Acutect and determined that at clinical levels neither drug increased Acutect's platelet inhibitory effect.

Preclinical studies indicated that Acutect is mainly metabolized and eliminated by the kidneys and that increasing renal dysfunction had a large effect shifting the route of elimination of Acutect to hepatobiliary excretion.

Toxicologic studies reported a decrease in spleen weight seen in the mouse and rabbit on acute studies and the rat in a chronic study. The clinical meaning is unknown.

Carcinogenicity studies were not done. A waiver was requested for reproductive toxicology studies. An evaluation of immunogenicity using guinea pigs did not reveal any antigenicity. Acutect was assessed for perivascular irritation and was found to be non-irritant.

Chemistry:

The reviewer, Q. Salako, indicated that there were no significant chemistry problems and that the product had been tested using all marketed generators (world/North America)?

Clinical:

In the two main efficacy studies, 280-32A and 280-32B, 25% of the patients had a history of deep venous thrombosis and 62% were using heparin or other anticoagulants.

Comment: The results suggest that Acutect is more likely to detect thrombosis in heparin treated patients. Since these patients are receiving heparin they are very recently diagnosed and the thrombophlebitis is likely more acute than patients receiving other anticoagulant therapy. The sponsor has not determined whether heparin might influence the Acutect images. Acutect is most likely to be used before anticoagulant therapy is begun and it is important to be able to understand the performance of Acutect before and during anticoagulant therapy.

The statistics review noted that the sponsor's hypothesized agreement rate of 60% (between the CV and Acutect readings) using the confidence interval analysis approach that was established in the Phase 3 protocol, failed to reject the null hypothesis with all six readers in study 280-32B and with three readers in study 280-32A.
Comment: It is not clear to this reviewer why the sponsor chose a level of 60% agreement between the standard of truth (CV) and Acutect. A higher rate of agreement should be required to establish the efficacy of a drug that is intended to detect the presence of thrombosis in patients presenting with the clinical features of thrombophlebitis.

The reviewing medical officer, Dr. Joseph Zolman, identified the following concerns.

Efficacy:
The descriptive image data was not detailed enough to determine what was observed by the blinded readers that allowed them to call an imaging result positive for the presence of thrombus.
Dr. Zolman made the statement that: "The image cannot differentiate between thrombus, thrombophlebitis, nonspecific uptake unrelated to thrombosis or phlebitis and--blood pool--".
Comment: I agree that the efficacy findings provided by the pivotal studies are non-specific. The product is seen throughout the soft tissue of the pelvis and lower appendages. There is a diffuse increase in radioactivity in the affected limb that undoubtedly is indicative of the hyperemia associated with an inflammatory response in the presence of thrombophlebitis in the cases presented.

The studies did not prove that acute thrombosis could be differentiated from the presence of chronic thrombus.
Comment: I agree since only patients with onset of symptoms of thromboplebitis within 10 days were studied. The imaging features of chronic phlebitis are unknown and may or may not be different between the acute and chronic states.

Specificity cannot be determined.
Comment: Only patients with the clinical presentation of thrombophlebitis were entered into the studies.

Safety:
Dr. Zolman noted that there was a small effect on both diastolic and systolic blood pressure as well as some elevation of glucose in about 20% of the patients and clinically significant elevation in ALT, AST or GGT in about 10% of patients. There was no followup of these patients to determine the resolution of these abnormalities thus these findings were inconclusive. The

statistical reviewer M. Sobhan noted in regard to the blood pressure and pulse rate changes that there was less than a 1% change in these parameters that were noted to be clinically significant at any time point after dosing. The elevated liver enzymes observed at 3 and 24 hours post dose were abnormal at baseline and the changes were not sufficient to implicate Acutect as the cause.
Comment: In the Phase 3 safety study, 280-33, conducted in 107 evaluable patients, there were no significant changes in either systolic or diastolic blood pressures.

It is very likely that this peptide diagnostic agent could be used on more than one occasion in the same patient.
It is essential to establish the immunogenicity that may develope in patients with repeated doses.

Conclusions:

Safety

1. Only single dose studies were conducted for this peptide agent. The assessment of immunogenicity was not adequate and the safety of repeated diagnostic administrations was not considered and remains unknown.
2. Abnormal blood pressure and clinical chemistry values were unsatisfactorily resolved. Further clarification of the safety profile of Acutect regarding liver enzyme studies is needed.
3. Acutect is eliminated and possibly metabolized by the kidneys. No studies were conducted in patients with severely reduced renal function.
4. An in vitro study conducted by the sponsor demonstrated that Acutect and all the peptides associated with Acutect inhibited platelet function. No in vivo manifestation of this observation was noted in the clinical trials even in the presence of Aspirin or heparin.
5. Safety monitoring (vital signs and adverse events) was conducted up to 180 minutes which may be too short an interval.

Efficacy

1. The possible detection of thrombosis by Acutect is a pathophysiological (functional) event, while contrast venography (CV) localizes an alteration in the venous lumen, an anatomical change. CV is a standard of truth that depends on detecting a loss of venous patency (blood flow) that is difficult to compare with Acutect which depends on detecting increased radioactivity at the site of thrombosis. The

ideal comparator, but an unrealistic one, would be the histopathologic confirmation of thrombosis.

2. The descriptive image data is not adequate to allow the reviewers to identify what the blinded readers saw that allowed them to identify the presence of thrombosis and to distiguish thrombus from phlebitis.
3. The ability of Acutect to distinguish between thrombus and phlebitis has not been demonstrated. The GP11b/111a receptors to which Acutect may bind are present on both activated platelet and endothelial cell surfaces.
4. The ability of Acutect to differentiate acute from chronic thrombosis has not been shown by the sponsor's studies.
5. Specificity could not be determined since only patients with the clinical presentation of thrombophlebitis were entered into the studies.
6. The marketed technetium ^{99m}Tc pertechnetate generators used in the clinical studies were not identified.
7. The sponsor has not determined whether heparin might influence the Acutect images. It is important to be able to understand the performance of Acutect before and during anticoagulant therapy.
8. The sponsor chose a level of 60% agreement between the standard of truth (CV) and Acutect. A higher rate of agreement should be required to establish the efficacy of a drug that is intended to detect the presence of thrombosis.

Recommendation:
Acutect is not approvable for the detection of thrombosis. It does demonstrate the presence of phlebitis but the specificity is unknown.

/S/ 12/11/97

APPEARS THIS WAY
ON ORIGINAL

A. Eric Jones M.D.
Clinical Team Leader HFD-160

CC:
CSO: C. Ferre-Hockensmith
NDA 20-887
Div File
Deputy Director: V. Raczkowski M.D.

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

(NDA)/PLA/PMA # 20-887 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-160 Trade and generic names/dosage form: ACUTECT KIT FOR THE PREPARATION OF TECHNETIUM TC 99M APCITIDE Action: (AP) AE NA

Applicant DIATIDE, INC. Therapeutic Class IP

Indication(s) previously approved _____
Pediatric information in labeling of approved indication(s) is adequate ___ inadequate ___

Indication in this application _____ (For supplements, answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

___ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___ c. The applicant has committed to doing such studies as will be required.
- ___ (1) Studies are ongoing,
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

✓ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. **If none of the above apply, attach an explanation, as necessary.**

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

/S/
Signature of Preparer and Title

9/10/97
Date

cc: Orig (NDA)/PLA/PMA # 20-887
HFD-160 /Div File
NDA/PLA Action Package
HFD-006/ SOlmstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

(NDA)/PLA/PMA # 20-887 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-160 Trade and generic names/dosage form: Neutect™ 100 ug peptide Action: AP (AE) NA

Applicant Diatide, INC Therapeutic Class 1P

Indication(s) previously approved _____
Pediatric information in labeling of approved indication(s) is adequate ___ inadequate ___

Indication in this application _____ (For supplements, answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

___ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___ c. The applicant has committed to doing such studies as will be required.
___ (1) Studies are ongoing,
___ (2) Protocols were submitted and approved.
___ (3) Protocols were submitted and are under review.
___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. **If none of the above apply,** attach an explanation, as necessary.

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

/S/ 2/15/98
Signature of Preparer and Title Date

2/18/98

cc: Orig NDA/PLA/PMA # 20-887
HFD-160 /Div File
NDA/PLA Action Package
HFD-006/ SOlmstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)